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BULLETIN ON ADVERSE DRUG REACTIONS

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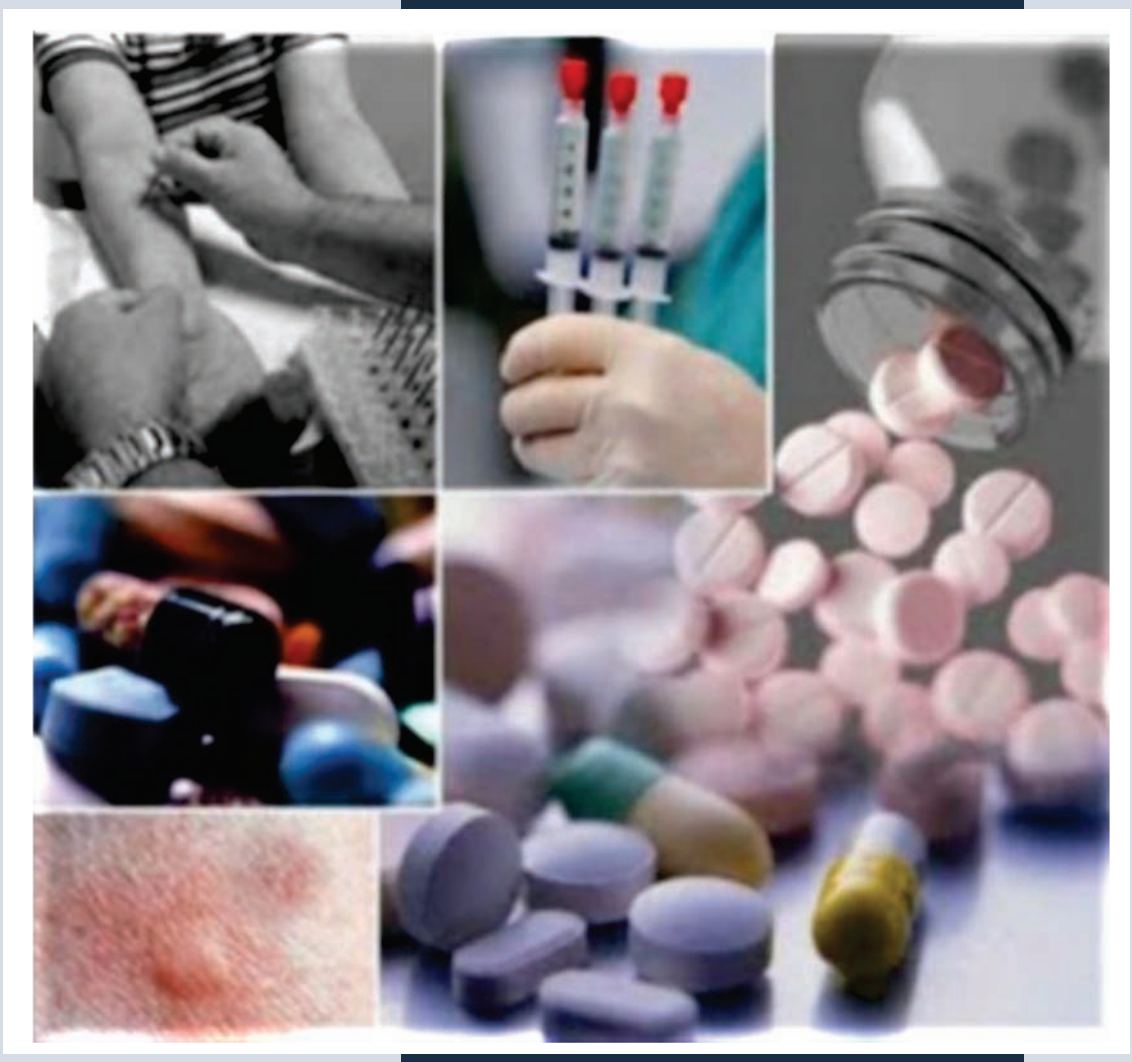

DEPARTMENT OF PHARMACOLOGY,

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Committee Members for Bulletin on Adverse Drug Reactions

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From the Editor's Desk . . . . ✍

Dear friends and colleagues,

I am extremely pleased to release the third issue of Bulletin on Adverse Drug Reaction of the year 2019.

Surprisingly some drugs routinely used for treatment of multiple diseases have detrimental effects on the bone health of patients. The review article of drug induced osteoporosis will give us an overview about this issue & highlight preventive & treatment strategies for the same. Nutraceuticals may be used to improve health, delay the aging process, prevent chronic diseases, increase life expectancy, or support the structure or function of the body. With the growing market and varied clinical applications it is important to be aware about their health hazards also. Hence our second review article intends to provide insight about the adverse reactions associated with nutraceuticals.

Hematological adverse effects of drugs are commonly encountered in clinical practice. The same is highlighted by an interesting case from our hospital on "IVIG induced hemolytic anemia". Apart from this the latest regulatory updates, a puzzle & an interesting exercise of match the column are the other highlights of the issue.

I sincerely hope that this issue will enlighten the readers regarding adverse drug reactions.

Finally, I would like to thank all the clinical departments of our institute for their valued contribution to pharmacovigilance and to the authors for contributing in the bulletin. I would also like to thank all the members of department of Pharmacology for their hard work in unfolding our current issue of this bulletin.

Thank you,

Dr. Sudhir Pawar

DRUG INDUCED OSTEOPOROSIS

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Introduction

Osteoporosis is characterized by abnormally low bone mineral density leading to impaired bone tissue structure and a rising risk for pathological fractures. WHO defines osteoporosis as spinal or hip bone mineral density (BMD) of 2.5 standard deviations or more below the mean for healthy individul as measured by Dual Energy X ray Absorptiometry DEXA.[1]

Fractures occurring due to osteoporosis are a major public health problem with about a million cases occurring each year worldwide. Osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds and 1 in 3 women and 1 in 5 men are at risk of an osteoporotic fracture.[2] In 2013, estimates suggested that ~50 million people in India had *T*-scores of <-1.3 The prevalence data of osteoporosis in India indicates that of the 230 million over 50 years of age in 2015, 20% are osteoporotic women.[3]

Osteoporosis can occur because of failure to achieve peak bone mass and excessive bone resorption and/or decreased bone formation during remodelling which invariably contributes to osteoporosis. There are two main types of osteoporosis primary osteoporosis which is the most common form and secondary osteoporosis which occurs due to other comorbid conditions or medications.[4]

Risk factors[5]

The aetiology of osteoporosis is multifactorial which is depicted in Table 1. The most common risk factor is age-related and female sex.

Table 1: Risk factors for Osteoporotic fractures

Non-modifiable	Modifiable
Advancing age	Premature menopause (<45 years)
Female sex	Amenorrhea (>1 year)
Family history (first degree relative)	Low body mass index
White Race	Sedentary lifestyle or prolonged immobilization
Previous fragility fracture	Low calcium intake
Rheumatoid arthritis	Low Vitamin D intake
Past glucocorticoid use	Alcohol consumption > 3 drinks/day
Past cigarette use	Low bone mineral density
	Medications

Among the modifiable factors, many widely used medications cause a decrease in BMD and increase risk of fractures. Drug induced osteoporosis is common and has a considerable impact on morbidity & mortality of patients suffering from chronic diseases for which drug interventions are essential. [6]

Diagnosis

The diagnosis of osteoporosis is based on measurement of BMD, which can be measured by central DEXA, peripheral DEXA, quantitative ultrasound densitometry. Amongst all these DEXA is the most accurate method to estimate fracture risk in postmenopausal women & men more than 50 years of age.

Management of Osteoporosis

1) **Non-pharmacologic treatment** – Lifestyle modification including smoking cessation. Physical activity among young women is essential for achieving peak bone mass. Drug profiles should be reviewed especially with drugs known to have adverse effects on bone health. Adequate Vitamin D and calcium levels are important for maintaining good bone health.

2) **Pharmacological treatment** - Several drugs have been approved for treatment of drug induced osteoporosis along with Vitamin D & calcium supplementation but only bisphosphonates, teriparatide and denosumab have been studied.

Medications causing bone loss [4]

General mechanisms involved in drug induced bone loss are

1) An increased osteoclastic activation with high bone-turnover state
2) Suppression of osteoblastic new bone formation
3) Inhibition of normal osteoid mineralization

- ***Glucocorticoids (GCs)*** [6]

Glucocorticoids are widely used in the treatment of inflammatory and autoimmune diseases. Glucocorticoid induced bone loss is the most common form of secondary osteoporosis. Around 30 - 50% of patients receiving GCs develop fractures.

Mechanism - GCs cause bone loss by direct osteocyte apoptosis leading to decrease in BMD. They reduce the recruitment of osteoblast differentiation and function thereby inhibiting bone formation. They primarily affect cancellous bone leading to significant risk of vertebral fractures. The indirect effects include reduced calcium resorption, suppression of growth hormone and altered sex hormones. Postmenopausal women and elderly men are at higher risk of developing osteoporosis when doses >20 mg daily are used.

Treatment [7] – Various guidelines proposed by American college of Rheumatology (ACR), International Osteoporosis Foundation (IOF) for prevention and treatment of GC induced bone loss recommend Vitamin D and calcium supplementation for all patients with GC-induced bone loss. Drug discontinuation or dose reduction is the first step towards management of GC-induced bone loss. Bisphosphonates are currently the standard therapy for prevention & treatment of GC-induced bone loss. Bisphosphonates like alendronate, risedronate are primarily used in men and postmenopausal women with GC-induced bone loss. For patients who cannot tolerate oral bisphosphonates IV zoledronic acid is an alternative. Premenopausal women, young patients, patients with T-score of 3.5 or below, resistant to bisphosphonates are given teriparatide. Monitoring of response to treatment is done by measuring BMD (DEXA) of the lumbar spine and hip.[8]

- ***Anti-coagulants***

Anticoagulants are widely used for the treatment of thromboembolic events and in stroke prevention. Long term therapy with heparin and oral anti-coagulants is associated with reduction in BMD and increased fracture risk.[9]

Mechanism [6] - Unfractionated heparin (UFH) inhibits osteoblast differentiation and function, leading to decreases in bone formation and increased bone resorption by inhibiting the expression of osteoprotegerin, receptor for receptor activator of nuclear factor- kappa B ligand. Both UFH and Low Molecular Weight Heparin (LMWH) treatment produce a dose-dependent decrease in serum alkaline phosphatase (a marker of bone formation), whereas only UFH causes a transient increase in urinary type I collagen cross-linked pyridinoline. (PYD, a marker of bone resorption). Newer heparins like fondaparinux does not cause bone loss and may be considered as an alternative to heparin in osteoporotic patients.

Warfarin inhibits the gamma-carboxylation of osteocalcin (a major protein of bone); non-carboxylated osteocalcin cannot bind to calcium effectively. Hence, the risk of hip fracture in women with high serum concentrations of non-carboxylated osteocalcin is higher than in women with low concentrations.[10]

Treatment - There are no published guidelines for prevention & treatment of heparin/oral anti-coagulant induced bone loss. LMWH and fondaparinux should be preferred over UFH in addition to Vitamin D & calcium supplementation.

- ***Thyroid hormone*** [10]

Overt hyperthyroidism is associated with accelerated bone remodeling, reduced bone density, osteoporosis, and an increase in fracture rate. Thyroid hormone T4 (levothyroxine) is administered in replacement doses for the treatment of hypothyroidism and in higher doses (suppression therapy) to patients with thyroid cancer.

Mechanism – T4 increases bone resorption directly and indirectly by inducing the production of bone-resorpting cytokines. TSH was reported to inhibit bone resorption directly, suggesting that suppression of TSH itself may cause bone loss.

Treatment – No specific guidelines for prevention & treatment of bone loss due to thyroid hormone. Anti-resorptive drugs therapy will help reduce fracture risk along with Vitamin D and calcium supplementation.

- ***Medroxyprogesterone acetate*** [11]

Medroxyprogesterone acetate DMPA widely used for the treatment of endometriosis and as a contraceptive agent, is associated with bone loss.

Mechanism- Due to the reduction in oestrogen, DMPA induces bone loss similar to pregnancy, with a decrease of 2–8% in BMD. The potential loss of bone owing to DMPA-related estrogen deprivation is of particular concern for teenage girls and women younger than 30, a time when BMD normally increases. Prolonged use could potentially decrease the peak bone mass and increase the risk of fragility fractures in 20-30 years. Most studies have shown that DMPA-induced bone loss is reversible, with improvement occurring quicker in the spine than the hip.

Treatment - The degree of recovery and the ultimate bone density after discontinuation may depend on patients age at initiation of the medication. All DMPA users should have vitamin D levels checked and calcium and vitamin D supplements given. Patients should be encouraged to exercise, stop smoking, and limit alcohol intake. Studies have shown that prescribing low-dose estrogen replacement to DMPA users can prevent bone loss in premenopausal women on DMPA.

- ***Aromatase inhibitors*** [7]

Aromatase inhibitors (AIs), including letrozole, anastrozole and exemestane, provide effective adjuvant hormone therapy for estrogen-receptor positive breast cancer in postmenopausal women. AIs inhibit the peripheral conversion of androgens to estrogens, resulting in lower estrogen levels and promote accelerated bone loss.

Mechanism - Estrogen suppresses bone resorption by increasing osteoclast apoptosis and reducing the number and activity of osteoclasts. It also promotes bone formation by reducing osteoblast apoptosis and promoting osteoblast differentiation. Residual estrogen levels in postmenopausal women are associated with bone density and fracture risk; lower levels equal higher fracture risk. Therefore, it is not surprising that medications that disrupt sex steroid production and lower estrogen levels are associated with negative effects on bone.[12]

Treatment - There is good evidence supporting the use of antiresorptive agents in the management of bone loss in patients on AIs. Ibandronate, risedronate, zoledronic acid, and denosumab have been

shown to prevent bone loss or increase BMD in women with breast cancer treated with AIs. Denosumab has been approved for treatment of osteoporosis related to androgen deprivation therapy of prostate cancer.

- ***GnRH agonists*** [12]

Gonadotropin-releasing hormone agonists (GnRHs) like leuprolide, goserelin, triptorelin, and histrelin are used to treat polycystic ovary syndromes, endometriosis, uterine myomas, breast cancer in premenopausal women, and prostate cancer.

Mechanism - GnRH agonists suppress estrogen levels and cause bone loss with an observed decrease of about 6%/year in BMD. One large retrospective cohort study of more than 50,000 men observed an increased risk of fracture in men receiving androgen deprivation therapy for the management of prostate cancer.

Treatment - Intravenous bisphosphonates like zoledronic acid, pamidronate and oral bisphosphonate have been proven to be efficacious in preventing bone loss in this patient population. Selective estrogen receptor modulators (SERMs) like toremifene and raloxifene have also been shown to be efficacious. Most recently, separate placebo-controlled trials of toremifene and denosumab have demonstrated vertebral fracture risk reduction in osteopenic men receiving androgen deprivation therapy, including GnRH agonists. Current recommendations, in addition to calcium and vitamin D supplementation, include DEXA evaluation.

- ***Proton Pump Inhibitors*** [10]

Proton pump inhibitors are commonly used in the treatment of diseases of the upper gastrointestinal tract.

Mechanism – The inhibition of proton pumps on the osteoclast ruffled border may decrease bone resorption. On the other hand, they decrease intestinal calcium absorption and increase bone resorption in vivo leading to decrease in BMD at the lumbar spine and hip. Impairment of calcium absorption occurs due to achlorhydria.

Treatment – There are no evidence- based practice guidelines addressing measures to reduce fracture risk in patients on PPIs. Effective treatment includes dose reduction to the shortest possible period of time and lowest effective dose. Alternatively, H2- blockers can be used where possible.

- ***Thiazolidinediones*** [13]

Thiazolidinediones are insulin-sensitizing drugs used for the treatment or prevention of type 2 diabetes mellitus. Thiazolidinediones like pioglitazone and pioglitazone, are selective agonists of peroxisome proliferator-activated receptor - γ

Mechanism - The activation of peroxisome proliferator - activated receptor (PPAR) - γ by thiazolidinediones (TZDs) stimulates adipogenesis, thereby regulating a number of cellular signaling pathways involved in bone metabolism. Differentiation of mesenchymal stem cells into osteoblasts is affected by preferential differentiation of mesenchymal stem cells into adipocytes. Reduced osteoblastogenesis indirectly modulates osteoclastogenesis. Altered maturation of mesenchymal stem cells, in concert with humoral factors, shifts the balance between bone formation and resorption Long term treatment with thiazolidinediones increases fracture risk by 4-fold in postmenopausal women & men.

Treatment – It is important to consider that Type 2 diabetes mellitus is itself a risk factor for inducing fractures. Addition of TZDs increases the risk further and hence should be used with caution. Discontinuation of the drug may be the most effective intervention to prevent thiazolidinedione induced fractures. Therapy aimed at thiazolidinedione-induced fracture prevention should include a detailed risk assessment, adequate calcium and vitamin D supplementation, nonpharmacologic therapy counselling, and possibly prescription therapy with bisphosphonates and teriparatide.

- ***Anti-depressants*** [14]

Selective serotonin reuptake inhibitors (SSRIs) & Tricyclic Anti-depressants (TCAs) are currently used for the treatment of depression. The serotonergic system plays an important role in bone physiology.

Mechanism – Serotonin appears to modulate skeletal response to parathyroid hormone through receptors and transporters found on osteoblasts & osteocytes. Gut-derived serotonin acts as a hormone to inhibit bone formation by binding to its receptor on osteoblasts, while serotonin in the brain acts as a neurotransmitter to stimulate bone formation and reduce bone resorption by suppressing sympathetic nervous system activity to bone.

Treatment - The risk of potential fracture should be balanced against the benefits gained from treating depression, especially in older persons who are already at increased risk for osteoporosis and fracture. Counselling regarding fall prevention, adequate calcium and vitamin D supplementation, and smoking cessation, are important lifestyle changes that may prevent fracture. Also BMD testing in patients receiving SSRIs, especially when other risk factors for fracture are present, such as advanced age or prior history of fragility fracture is advisable.

- ***Anti-epileptic drugs*** [15]

Antiepileptic drugs (AEDs) constitute the main-stay of treatment of epilepsy. High incidence of adverse effects is a major limitation with AEDs with major concern of its significant metabolic effects on the bone.

Mechanism – Many AEDs (phenobarbital, phenytoin, carbamazepine) increase the activity of P450 enzymes leading to increased catabolism of vitamin D to inactive metabolites and a subsequent rise in Parathyroid hormone (PTH) which increases the mobilization of bone calcium stores and subsequent bone turnover. In ambulatory patients, long-term antiepileptic therapy has been associated with low bone density and an increase in fractures. The increase in fracture rate is due to both seizure-related injuries and the adverse effects of AEDs on bone strength.

Treatment - Evidence-based strategies regarding prevention and monitoring of bone diseases in patients on AED therapy are needed. Prophylactic Vitamin D supplementation up to 2000 IU/day for patients at risk treated with liver enzyme-inducing AEDs and valproate. Calcium intake in doses of 600–1000 mg/day should also be ensured. Bisphosphonates are usually reserved for the treatment of high fracture risk patients. Patients on long-term AEDs should be screened DEXA scan or FRAX analysis.

- ***Calcineurin Inhibitors*** [6]

Calcineurin inhibitors, including cyclosporine (CsA) and tacrolimus (FK506), have been widely used as immunosuppressive agents to prevent organ transplant rejection and for autoimmune disorders.

Mechanism - In vitro, calcineurin inhibitors inhibit osteoclastogenesis and osteoclast activity via reductions in Nuclear Factor of Activated T-cells, cytoplasmic 1 (NFATc1). There are indirect effects on osteocalcin & vitamin D metabolism, leading to secondary hyperparathyroidism and subsequent high bone turnover osteopenia.

Treatment – Along with Vitamin D & calcium supplementation, bisphosphonates are given for the treatment of calcineurin inhibitor induced bone loss.

Other medications leading to fewer incidences of bone loss and fractures are listed in Table 2. [4]

Conclusion

Drugs routinely used for treatment of multiple diseases have detrimental effects on the skeleton. Awareness of this clinical problem is limited, and consequently, preventive measures are often not undertaken. Adequate monitoring of bone health and therapeutic intervention are recommended when drugs with an adverse bone safety profile are used, particularly in patients with additional risk factors for osteoporosis. Further studies are needed to determine the best prevention and treatment strategies for many drugs that increase bone loss or fractures.

Table 2: Other Medications causing Osteoporosis

Medications	Mechanism of Bone loss
Chemotherapeutic agents Methotrexate, Ifosphamide, Imatinib	Directly cause bone loss,bone loss secondary to renal tubular phosphate wasting and loss due to negative effects on gonadal tissues.
Vitamin A & Retinoids	Inhibit osteoblast activity,stimulate osteoclast formation and counteract the ability of vitamin D to maintain normal serum calcium concentrations, thereby leading to accelerated bone resorption and fractures
Loop diuretics	Inhibit sodium and chloride reabsorption and consequently inhibit calcium reabsorption, increasing its renal excretion and bone turnover.
Ethanol	Direct toxic effects on osteoblastic function with low serum osteocalcin and on osteoclasts with increased resorption & increased urinary pyridinolines.
Anti-retroviral therapy	Bone loss occurs by increasing osteoclastogenesis and bone resorption, and by causing mitochondrial damage, impairing osteoblastic function and bone formation leading to a decrease in BMD.
Aluminium (Antacids)	Inhibition of bone mineralization, impairment of osteoprogenitor/osteoblast proliferation and osteoblast number & reduction of PTH secretion.
Lithium	Inhibits inositol phosphate metabolism and influx of extracellular calcium into the parathyroid cells resulting in increased PTH secretion in response to this low intracellular calcium.

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ADVERSE DRUG REACTIONS DUE TO NUTRACEUTICALS

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The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" in 1989 by Stephen DeFelice, MD, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ. According to DeFelice, a nutraceutical can be defined as, "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease." [1] Nutraceuticals represent nutritional components that provide therapeutic or physiological benefits beyond the basic nutritional needs and include a wide range of compounds. They are nutrients from natural sources with pharmaceutical-like effects. [2]

Nutraceuticals can be grouped into the following three broad categories [3]:-

1. **Nutrients**: - Substances with established nutritional functions, such as vitamins, minerals, amino acids and fatty acids.
2. **Herbals**: - Herbs or botanical products as concentrates and extracts (e.g. Ginkgo, St. John's wort, Ginger).
3. **Dietary supplements: -** Reagents derived from other sources (e.g. pyruvate, chondroitin sulphate, steroid hormone precursors) serving specific functions, such as sports nutrition, weight-loss supplements and meal replacements.

More and more physicians are realizing the need to supplement their medical treatment with a good, balanced diet and nutra products. In most healthcare facilities, focus is given not just to prescribing the right medication but also on offering the right food for quick and effective recovery of patients. Chronic diseases need more than just the traditional pharmaceutical approach. Our food and nutrition expertise can help create a new industry where nutrition plays a bigger role in helping people who live with difficult chronic medical conditions. With the changing disease pattern and lifestyle diseases, consumers are shifting towards prevention. The utilities of both medicines and food products inclusive of nutraceutical products today coexist for the complete wellness of a patient/consumer. Usually for chronic diseases, physicians make patients aware of lifestyle changes and advise them to make the necessary changes in their lifestyle and diet.[4]

This field is currently experiencing a renewed impetus as several food components are now being employed as medicines, either directly or as prodrugs. Indeed, there are areas in which the border between "food" and "pharma" is not well defined, as the former often contains several bioactive compounds, including secondary plant molecules (polyphenols), fibers, friendly bacteria, essential fatty acids, probiotics and other contributors. Currently, there are several drugs that are derived from natural products, including those which humans have been exposed to via diet. Hence, it is sometimes

difficult to distinguish between bioactive molecules termed "drugs" and other substances that are classified as "nutrients."[4]

Challenges faced by the food sectors [4]

***Chances of self-medication*:** As there is increasing awareness among people about the perceived health benefits these products offer for preventing or treating some major health disorders, there may be a chance that patients start self-medicating. Such patients may be exposed to the quality issue for that particular nutra product as well, instead of turning to the much needed medical assistance.

***Evolving regulatory compliances*:** Globally, the focus is upon having pertinent regulations that are made with guidance for policy makers over high-quality scientific, technical, and regulatory nuances.

***Appropriate claims*:** Manufacturers should be careful when marketing their products so they do not make claims that can be misleading and false. Regulatory bodies now place emphasis on the importance of science based claims that do not mislead the consumer in any way.

***Misleading advertising and promotions*:** Although it is related to health claims and their promotion to consumers, irresponsible advertising may end up misleading the consumer. For consumers, safety, quality, and effectiveness are the topmost concerns. There are advertising guidelines and compliances that should be enforced.

Nutraceutical regulations [5]

Nutraceutical products are widely available and monitored with the same level of scrutiny as "dietary supplements". Food Safety and Security (FSS) Act was passed by the parliament in 2006. In 2008, Food Safety and Standard Authority of India (FSSAI) came into existence. The FSSAI has prepared the draft rules and regulations for implementation of FSS Act 2006, Rules and Regulation 2011 section 22(1) of FSSA define food for special Dietary uses. The draft regulation would be sent for notification for The FSSAI will make rules and frame standards to regulate nutraceuticals as outlined in the Food Safety Act, 2006.

ADRs of Nutraceuticals

As the global use of nutraceuticals has increased for humans, so have health risks emerging from active components as well as from toxic contaminants of supplements. Since these nutraceuticals have not been tested as rigorously as pharmaceutical drugs and no large-scale clinical trials have been done, safety remains a serious issue. Currently, it is a common practice that those receiving prescription drugs also consume nutraceuticals and some nutraceuticals are likely to alter efficacy and safety of pharmaceutical drugs by modulating their pharmacodynamics and pharmacokinetics.

1) Vitamin Supplements [6]

Fat soluble vitamins

- **Vitamin A -** Acute toxicity of vitamin A following doses of 50,000 units is characterized by nausea, vomiting, headache, vertigo, blurred vision, muscular incoordination. Chronic use of high-dose vitamin A can cause lethargy, irritability, anorexia, abdominal discomfort, nausea and vomiting, excessive sweating, itching, redness, and hyperpigmentation.
- **Vitamin E** - In healthy adults, doses of 200–800 mg/day of vitamin E may cause gastrointestinal upset, 800–1200 mg/day may induce antiplatelet effects and bleeding and doses above 1200 mg/day have resulted in emotional disturbances, thrombophlebitis, altered serum lipid levels, thyroid effects and gonadal dysfunction.
- **Vitamin D -** Excessive vitamin D intake causes toxicity which includes hypercalcemia, reversible renal impairment, anemia, osteoporosis, decreased growth in children, weight loss, photophobia, metastatic calcification, pancreatitis, generalized vascular calcification, seizures and psychosis.
- **Vitamin K –** Painful swelling at injection site, transient flushing, dizziness, increased risk of bleeding; rarely hyperbilirubinemia, liver damage in children and hemolysis.

Water soluble vitamins

- **Folic acid -** It is well tolerated in doses less than 1 mg/day. Doses of 5 mg/day can cause abdominal cramps, diarrhea, and rash. Large doses of folic acid (>15 mg/day) can cause altered sleep patterns, irritability, confusion, exacerbation of seizure frequency, nausea, and flatulence.
- **Niacin -** Itching, increased intracranial blood flow and headache can occur with doses of niacin over 30 mg/day, commonly used for treatment of hyperlipidemia. Large doses of niacin can cause gastrointestinal symptoms including nausea, vomiting, bloating, anorexia, diarrhea, and peptic ulcers.
- **Vitamin C -** The acute adverse effects of oral vitamin C are dose-related and include nausea, vomiting, esophagitis, heartburn, abdominal cramps, gastrointestinal obstruction, fatigue, flushing, headache, insomnia, sleepiness, and diarrhea when several grams are taken at once. Long-term intake of vitamin C may cause precipitation of urate, oxalate, or cysteine stones or drugs in the urinary tract.
- **Vitamin B6** - Itcan cause nausea, vomiting, abdominal pain, headache, somnolence, allergic reactions and breast soreness or enlargement.
- **Vitamin B12 –** It can cause diarrhea, peripheral vascular thrombosis, itching, urticaria, and anaphylaxis**.** Vitamin B12(20 µg/day) and pyridoxine (80 mg/day) may cause rosacea fulminans, characterized by intense erythema with nodules, papules, and pustules.

2) Fish Oil and Omega-3 Fatty Acids

The simultaneous consumption of fish liver oils which also contain vitamin A and multivitamin supplements could result in hypervitaminosis. Furthermore, fish oils and omega-3 fatty acid supplements may exacerbate anticoagulation and promote bleeding in patients taking anticoagulant medications such as warfarin.[7] [8]

3) Weight-loss, Sports and Bodybuilding Supplements

One of the compounds that has recently been widely incorporated in sports supplements is 1,3-dimethylamylamine (DMAA). DMAA has further been banned as a performance enhancing drug by the World Anti-Doping Agency. Accidental intake of supplements with DMAA, mainly in children, have caused relatively mild adverse effects such as tachycardia, nausea, and vomiting. However, serious cardiovascular events after DMAA intake have also been reported. Body-building supplements are quite often adulterated with anabolic steroids that are modified variants of androgens designed to increase muscle mass. Adverse effects of anabolic steroids include cardiomyopathy, altered serum lipids, acne, swollen breast tissues in men and hepatotoxicity.[9]

4) Herbal Products [10]

Ginkgo biloba

It is commonly referred as "living fossil. The long-term use of *G. biloba*extract has been associated with spontaneous bleeding. Serious side effects, such as bleeding, hematoma, hyphema, apraxia, neurological deficits have been reported in humans from the concurrent use of *G. biloba*extract and anesthetics, analgesics, anticoagulant or antiplatelet agents.

Green Tea Extract (GTE)

Green tea (*Camellia sinensis*) extract is a commonly used beverage, nutraceutical, and phytopharmaceutical globally. Side effects of GTE in humans include bloating, nausea, heartburn, abdominal pain, dizziness, headache, muscle pain and hepatotoxicity.Evidence also suggests that increased consumption of green tea infusions may increase the risk for breast cancer.

Green Coffee Bean/Caffeine

Although coffee bean has a mixture of more than 1000 phytochemicals, caffeine is the most significant from a nutraceutical perspective. Blood concentrations of caffeine in excess of 30 ìg/mL are associated with clinical signs of intoxication, such as anxiety, restlessness, and tachycardia. The symptoms of acute and chronic caffeine intoxication after consumption of high doses (300–800 mg/person/day) have been described as caffeinism. These symptoms include dizziness, restlessness, agitation, anxiety, irritability, muscle tremor, hyperventilation, arrhythmia, tachycardia, and hypertension.

Kava

Kava (*Piper methysticum*), also known as kava kava, is an herbal shrub that has been used for centuries in the South Pacific as a social beverage and in traditional ceremonial rituals. Prolonged use of a dose equivalent to 400 mg or more of kava per day is likely to cause the characteristic skin lesions of kava toxicity (pigmented, dry, covered with scales) which heals upon discontinuation.

Aloe vera

It is a stem-less plant and the whole leaf extract contains more than 200 chemicals, including amino acids, vitamins, minerals, lignin and phytosterols. Use of topical *Aloe vera*is not associated with significant side effects, but its oral ingestion may cause abdominal cramps and diarrhoea and thereby decreasing the absorption of drugs.

St. John's Wort (Hypericumperforatum)

Extracts of this plant are known to have at least 150 compounds. The side effects related to this herb are gastrointestinal irritation, allergic reactions, tiredness, and restlessness. In some other cases, hypericum extract might have caused autonomic arousal, hepatocellular carcinoma and bone marrow necrosis.

Other herbal supplements and adverse effects are tabulated in table below. [11]

Sr.No.	Common name	Formal name	Benefits	Adverse effects
1	Ephedra *(ma huang)*	*Ephedra sinica*	Relieve nasal congestion and asthma, promotes weight loss and enhances athletic performance	Increases blood pressure and heart rate and can cause headache, insomnia, dizziness, seizures, arrhythmias and addiction.
2	Garlic	*Allium sativum*	Reduces cardiovascular Inhibits risk and serves asanti-inflammator	Can potentiate other platelet inhibitors or cause bleeding
3	Ginseng	*Panax ginseng*	Improves physical performance, energy level, cancer prevention and blood sugar reduction	Insomnia, diarrhea and hyperacidity
4	Yohimbe	Pausinystalia Yohimbe	Works as aphrodisiac and improves athletic performance	Increase anxiety, blood pressure, sleeplessness, tachycardia, tremors & vomiting
5	Black cohosh	Cimicifugarace-mosa	Improves menopausal symptoms, premenstrual syndrome & dysmenorrhea	Gastric discomfort
6	Ethinacea	Ethinacea-angustifolia	Stimulates immune response; wound healing; treats common cold and yeast infections	Immune suppression

Nutraceutical–Drug Interaction and Toxicity Outcome [10]

An interaction of a drug with food, herbs and dietary supplements can lead to serious outcomes due to multiple factors**.** Some nutraceuticals are known to inuence the drug metabolizing enzyme cytochrome P450 (CYP450) and/or transporters, and therefore can reduce or enhance the effects of therapeutic drugs.Multiple constituents of *Ginkgo biloba*extract induce the enzyme CYP450. Ginseng is a CYP450 inducer, while grapefruit juice is a CYP450 inhibitor.

- An example of pharmacokinetic interaction is the interaction between ginkgo and phenytoin. Ginkgo by increasing metabolism reduces the blood levels of phenytoin.
- St. John's wort extracts can upregulate and downregulate gut and hepatic CYP enzymes and xenobiotic transporters, and by these mechanisms it can alter the pharmacokinetics and efficacy of concurrent medications, such as theophylline, warfarin, verapamil, digoxin, ibuprofen, methadone, oxycodone, antidiabetic drugs.
- An example of a pharmacodynamic interaction is the one between Ma Huang and theophylline due to similar adverse effect profiles.
- Vitamin C in high doses can interfere with the anticoagulant effects of warfarin by reducing prothrombin time. In addition, vitamin C increases the absorption of iron, which may cause toxic effects, especially in children.[6]

Conclusion

The market for dietary supplements and nutraceuticals taken to improve the health or wellbeing of the customer is enormous. However, they are not necessarily safe for everybody. Like regular drugs, supplements with active ingredients that provide a physiological or pharmacological effect are likely to also cause adverse effects in susceptible individuals. More attention to adverse effects and potential interactions is needed in order to avoid serious medical outcomes. Users and physicians alike should consult updated literature before beginning or advising a regimen involving these substances. Medical providers should be aware that a large fraction of general population takes dietary supplements. They should, therefore, request information from patients about their supplement intake in order to provide optimal medical care.

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EVALUATION OF A CASE INTRAVENOUS IMMUNOGLOBULIN INDUCED HEMOLYTIC ANAEMIA

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Introduction

Guillain-Barré syndrome (GBS) is a rapidly progressive inflammatory demyelinating peripheral neuropathic disorder which can be treated either with intravenous immunoglobulin (IVIG) or plasmapheresis.[1] IVIG is a pooled preparation of normal human immunoglobulins obtained from several thousand healthy donors and its major constituent is IgG monomer(>96%), while another components like IgG dimers, IgM, IgA, auxiliary materials (maltose, sucrose, etc.) can be found in trace amounts.[2] It also contains IgG blood group immunoglobulins e.g. anti-A, anti-B or anti-D[3] IVIG infusions are used to treat many autoimmune, inflammatory conditions and immunoglobulin deficiency disorders.[4,5]

IVIG is life-saving in many conditions but it can lead to numerous adverse effects which include immediate reactions like flushing, urticaria, nausea, vomiting, etc. and delayed reactions such as septic meningitis, renal impairment, thrombosis, and hemolytic anemia which are serious and rare effects. [6] Hemolysis is a rare reported adverse reaction of immunoglobulin treatment.[7] The incidence of IVIG-associated hemolytic anemia cases is between 0.1-1%.[8,9] Hemolytic anemia is self-limiting in the majority of mild and moderate cases i.e hemoglobin> 8 g/dl but it could be serious if it remains unnoticed.[6,10] There are multiple reports of IVIG-induced hemolytic anemia in patients receiving high doses of IVIG (>2g/kg). However, only a few cases of hemolysis following administration of low-dose IVIG have been reported.[11]

Here we are reporting a case of IVIG induced hemolytic anemia in a patient with Guillain-Barré syndrome (GBS) which occurred at dose of 0.4g/kg (Total 30 gm/day).

Case

A 27-year-old male patient weighing 72 kg with blood group B positive (non O blood group) presented to the hospital with complaints of bilateral lower limb pain, followed by bilateral lower and upper limb weakness, tingling sensation in upper limbs and drooping of the left eyelid for 3 days. The patient had a history of upper respiratory tract infection 10 days back and a history of fall 4 days before hospital admission. Based on clinical findings and investigations, he was diagnosed with Guillain-Barré syndrome (GBS).

For GBS, treatment with Injection Immunoglobulin IV 0.4g/kg (Total 30 gm/day) once a day for 5 days was started. Other medications received by the patient were injectable ceftriaxone, pantoprazole,

ondansetron, and tablet azithromycin. After 4 days of initiation of IVIG therapy blood profile showed a gradual decrease in the hemoglobin level and peripheral smear examination reported normocytic normochromic anemia with few spherocytes. The liver function test showed raised indirect bilirubin level. Lactate dehydrogenase level was also found to be raised. Direct Coombs' test was also positive. Thus, suspicion of drug-induced hemolytic anemia was made. Treatment with IVIG was continued for 5 days i.e. full course was completed. After IVIG therapy, patient completely recovered within 10 days.

As per ICH E2 seriousness criteria, the reaction was serious as it was medically important. The causality of this reaction as per the WHO UMC causality assessment scale was "Possible", as the dechallenge was not done as the full course of treatment was completed. All other medications were continued during the recovery period, thus confirming it to be IVIG induced hemolytic anemia. According to the Modified Schumock & Thornton Preventability Scale, the occurrence of reaction in the case of our patient was "non-preventable".

Discussion

IV immunoglobulin(IVIG) is usually used in dose range 0.4-4g/kg[8] for many indications like primary immunodeficiencies, chronic inflammatory demyelinating polyneuropathy, Kawasaki disease, following bone marrow transplantation, prevention of bacterial infections in patients with hypogammaglobulinemia, idiopathic thrombocytopenic purpura, etc.[12] The usual IVIG regimen in GBS is 0.4 g/kg body weight per day for five consecutive days.[13] IVIG is generally well tolerated and safe, but approximately less than 5% of patients experience adverse effects. Some adverse effects such as thrombosis, aseptic meningitis, hemolysis, and renal failure are seen mainly with the use of high-dose IVIG. (e" 2g/kg) [9,14]

According to Canadian IVIG hemolysis Pharmacovigilance Group, IVIG associated hemolysis is defined as hemolytic events occurring within 10 days of administration of IVIG as evidenced by decrease in Hb of <10 g/L, positive Direct anti-globulin test plus at least two of the following criteria: elevated reticulocyte count, elevated serum lactate dehydrogenase, elevated serum unconjugated bilirubin, low serum haptoglobin, hemoglobinuria, hemoglobinaemia, or the presence of spherocytosis.[15]

The first mechanism by which IVIG can cause hemolysis is the presence of blood group antibodies namely, anti-A anti-B in IVIG products. As these preparations are made from pooled donors preferably from patients with blood group O, there are chances of the creeping in of anti-A, anti-B, and sometimes anti-D or other red blood cells (RBCs) antibodies in the product during the preparation that can cause direct antibody attack on RBCs. The second mechanism is enhanced erythrocyte sequestration as high molecular weight IgG complexes present in IVIG, can activate the complement system as they mimic immune complexes. These complexes bind to complement receptor 1 on RBCs which leads to erythrophagocytosis, and hence a reduction in hemoglobin.[16]

It is reported that patients with a non-O blood group as well as patients with a low concentration of soluble A and/or B substance in their plasma are at increased risk for hemolysis due to their inability to

neutralize the anti-A and/or anti-B isohemagglutinins present in the plasma after IVIG infusion. Other risk factors that seem to contribute to hemolysis are administration of high-dose IVIG, excessive titers of ABO antibodies contributing to the high final quantity of ABO antibodies in IVIG products. A case series of 5 patients of GBS with non O blood group reported by Nguyen et.al.found that patients receiving high-dose of IVIG i.e. 4 patients received 4 g/kg and 1 patient received 1g/kg developed clinically significant hemolytic anaemia.[18] A recent case of 10 month old infant with Kawasaki disease who was treated with high-dose IVIG and developed severe hemolytic anemia also confirms the risk of hemolysis in non O blood group patients with severe underlying inflammation. [19]

Individual patient factors, such as inflammatory state reflected by elevated ESR and/or CRP, have been hypothesized to increase the risk of hemolytic anaemia with IVIG administration.[20]

Patient-related factors that increase risk are Fc receptor polymorphisms, complement receptor polymorphisms, and antigen density on RBCs which determine the rapidity with which opsonized RBCs are removed from the circulation.[9,17]

All these risk factors like non O blood group and inflammatory underling pathology might have contributed to hemolysis despite of the low dose. A similar case of a 30 year old female patient with inflammatory myositis who received IVIG 0.4g/kg/day for 5 days and developed hemolytic anemia was also reported by K. Shah et al.[12]

Hemolytic anemia is self-limiting in the majority cases. However, in severe cases, (Hb< 8 g/dl) proper blood transfusion is needed. If the patient needs IVIG obligatory, then switching to another IVIG product which contain lower concentrations of antibodies.[21]As hemolysis associated with IVIG is usually due to ABO antibodies, reduction in the titers of these antibodies in IVIG helps to lower the frequency of hemolysis. It has been reported that the manufacturing methods that do not have precipitation steps will result in higher levels of isoagglutinin in the final IVIG product, and therefore, have an increased risk of IVIG-associated hemolysis. Hence, isoagglutinin reduction steps will be required to minimize the potential risk. Another measure to prevent hemolysis is IVIG recipients should be monitored closely for signs and symptoms of hemolysis. It is recommended to monitor Hb before IVIG infusion and 36–96 h post-infusion in patients at higher risk of hemolysis and low baseline Hb.[22]

Conclusion

Hemolytic anemia caused by IVIG is usually self-limiting and a small proportion may be clinically significant. Dose of IVIG, blood group of the patient and underlying inflammatory pathology should always be borne in mind when IVIG administration is started.

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PUBLISHED LITERATURE ON INTRAVENOUS IMMUNOGLOBULIN INDUCED HEMOLYTIC ANEMIA

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Intravenous immunoglobulin-induced haemolysis: a case report

Transfusion Medicine. 2014;24(4):219-26.

Desborough MJ, Miller J, Thorpe SJ, Murphy MF, Misbah SA.

Case report

We report a case of severe IVIg-induced haemolysis. Three days after administration of IVIg (0·4 g/kg for 5 days) for an exacerbation of myasthenia gravis to a blood group AB Rh D positive adult patient, the patient developed severe haemolysis and acute renal failure (creatinine 695 gm/L from a baseline of 68 gm/L prior to the infusion). Hemoglobin concentration (Hb) was 5.8 g/dL (baseline 12.3 g/dL), reticulocytes 10·4%, bilirubin 70 mol/L, LDH 2288 IU/L. The direct antiglobulin test (DAT) was positive for IgG and C3 (5+). A blood film revealed anaemia, polychromasia and spherocytosis. An indirect antiglobulin test (IAT) performed locally demonstrated anti-A1 of 128, anti-A2 of 16 and anti-B of 64. A diagnosis of IVIg-induced haemolysis resulting in severe haemolysis and dialysis-dependent acute renal failure was made. Treatment was supportive with O RhD positive red blood cell transfusions for symptom relief (3 units) and dialysis. The IVIg batch was quarantined pending further investigation. This batch continued to be used for low dose prophylactic treatment (e.g. 0·4 g/kg monthly) for other patients but not for high dose treatments. Aliquots of IVIg from the same batch as that received by the patient were sent to the National Institutefor Biological Standards and Control (NIBSC), along with samples of IVIg from other brands of IVIg. The patient's renal function recovered over 4 weeks. We suspect that both patient factors (blood group AB RhD positive) and IVIg-related factors (anti-A level at upper limit of acceptable range) played a role in causing severe haemolysis.

A Case Report of Intravenous Immunoglobulin (IVIG) Induced Haemolytic Anaemia

J Basic Clin Pharma 2017;8:S80-S82.

Shah KB, Makwana HD, Malhotra SD, Patel PR.

Case report :

A 30-year old female patient presented at emergency medicine department at our hospital with the chief complaints of severe body ache and weakness of bilateral upper and lower limbs. She was

diagnosed to be suffering from inflammatory myositis based on her investigations by her treating physician. She received 0.4 g/kg Intravenous Immunoglobulin (IVIG) (Total 120 gm given) and 1 gm IV methyl prednisolone once a day over a period of five days. In the reports after 2 days of initiation of IVIG therapy the blood profile showed decrease in the haemoglobin levels (3.75 gm/dl) and gradual increase in the total bilirubin levels. The patient was diagnosed with haemolytic anaemia due to IVIG by the consulting physician. The patient was transfused with 3 units of whole blood and started with oral prednisolone 1 mg/kg/day as a treatment of haemolytic anaemia. Gradually the haemoglobin level started to rise and went near the baseline level on 34th day of initiation of IVIG therapy.

Occurrence of hemolytic anemia in patients with GBS treated with high-dose IVIg.

Neurol Neuroimmunol Neuroinflamm. 2014 Dec 11;1(4):e50.

Nguyen TP, Biliciler S, Wahed A, Sheikh K.

There are no established guidelines on treating patients with Guillain-Barré syndrome (GBS) who relapse or do not improve after a standard course of treatment (IVIg or plasma exchange). Some centers will opt for a second course of the initial treatment. There is an ongoing trial of a second course of IVIg in patients with severe GBS. We retrospectively reviewed 4 patients with severe GBS who received high-dose IVIg. One patient inadvertently received a high dose of IVIg for Miller Fisher syndrome. All patients received a total of at least 2 courses of the standard dose of IVIg (total >4 g/kg). We review their clinical course and side effects.All patients with non-O blood types developed clinically significant hemolytic anemia requiring blood transfusion. Hemolytic anemia may limit doses of IVIg for treatment of severe GBS in patients with non-O blood types.

Hemolysis Associated with IVIG Therapy

Journal of Allergy and Clinical Immunology. 2016;137(2): AB257

Rubin, Tamar et al.

Intravenous immunoglobulin (IVIG) is used for treatment of various immune diseases. Although IVIG is known to contain antibodies to A and B antigens, these antibodies do not typically mediate clinically significant hemolysis. Our patient, with blood type A, developed symptomatic hemolysis soon after receiving multi-dose IVIG for treatment of interstitial lung disease. Hemoglobin (Hg), LDH, total bilirubin (TB), haptoglobin, reticulocyte count (RC) and a DAT were evaluated prior to IVIG infusion and for two weeks after infusion. Prior to our patient's IVIG infusion, his Hg was 14.3g/dL. His other hemolysis labs were unremarkable. He received 5 infusions of IVIG (each 35g) over the course of 3 days. Three days after his last IVIG infusion, his labs showed a drop in Hg to 11.4g/dL, an increase in LDH to 574U/L,TB 2.9mg/dL, haptoglobin.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by Dr. Bhagyashree Mohod * and Dr. Rajmohan Seetharaman **

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Ranitidine is safe. NMDA levels found in ranitidine are similar to the levels found in common foods

Background: The U.S. Food and Drug Administration had learned that some ranitidine medicines, contained a nitrosamine impurity called N-nitrosodimethylamine (NDMA) at low levels. NDMA is classified as a probable human carcinogen (a substance that could cause cancer) based on results from laboratory tests. NDMA is a known environmental contaminant and found in water and foods, including meats, dairy products, and vegetables. On 1/11/19 USFDA announced its testing results for NMDA in ranitidine.

Issue: *USFDA TESTS*: N-nitrosodimethylamine (NDMA) levels found in ranitidine are similar to the levels like common foods (like grilled or smoked meats etc) says USFDA. USFDA also conducted tests that stimulate stomach environment to check what happens to ranitidine if exposed to acid in the stomach with normal diet. Results indicate, NMDA is not formed through the process. If ranitidine is exposed to a stimulated small intestine environment, NMDA is not formed.USFDA also developed a stimulated gastric fluid (SGF) model to be used with the LC-MS testing method. The results of these tests showed no additional NMDA generated in the stomach.

USFDA ON TESTS BY THIRD PARTY: NMDA observed through FDA testing are much lower than the levels some third party scientists first claimed.

SETS PERMISSIBLE LIMITS: USFDA sets NMDA limits: Consuming up to 0.096 micrograms (96 nanogram) or 0.32 parts per million (ppm) of NMDA per day is considered reasonably safe for human ingestion based on lifetime exposure. This is based on methods described in the 2018 ICH Guidance M7(R1) Assessment and control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to limit Potential Carcinogenic Risk.

Why is it not a matter of worry?

As per 2018 ICH Guidance M7(R1), if people consume 96 nanograms of NMDA daily for 70 years, the probable risk of cancer would be 1 in 100,000 patients. Only if NMDA levels in ranitidine are above the acceptable limits (96 nanograms per day or 0.32 ppm). USFDA is asking companies to voluntarily recall ranitidine batches. If the NMDA levels are within permissible limits, it is safe for use. Several brands / companies have started selling and re-launching ranitidine in USA.

Reference: *Ranitidine Laboratory Tests. U.S. Food and Drug Administration. 2019 [cited 4 December 2019]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-ranitidine*

Cefotaxime: Risk of Angioedema

Background: The NCC-PvPI, IPC has advised the CDSCO to revise the Public Interest Litigation (PIL) for cefotaxime to incorporate angioedema as a clinically significant adverse drug reaction.

Issue: Cefotaxime is an antibacterial indicated for the treatment of infections, septicaemia and prophylaxis of surgical infections. Between July 2011 to July 2018, NCC-PvPI received 16 Individual case safety report (ICSRs) of cefotaxime associated angioedema. These cases were reviewed by Signal Review Panel (SRP), PvPI, IPC and a strong causal relationship between cefotaxime and angioedema was found.

Reference: *WHO Pharmaceuticals Newsletter. World Health Organization. 2019 [cited 4 December 2019]. Available from: https://www.who.int/medicines/publications/PharmaNewsletter5-19/en/*

Phenobarbital: Risk of DRESS syndrome

Background: The NCC-PvPI, IPC has advised the CDSCO to incorporate drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) as a clinically significant adverse drug reaction into the PIL for phenobarbital.

Issue: Phenobarbital is indicated for the treatment of epilepsy. Between July 2011 to December 2018, the NCC-PvPI received 12 ICSRs of phenobarbital induced DRESS syndrome. The cases were reviewed by SRP at the NCC- PvPI, IPC, and a strong causal relationship between phenobarbital and DRESS syndrome was found.

Reference: *WHO Pharmaceuticals Newsletter. World Health Organization. 2019 [cited 4 December 2019]. Available from: https://www.who.int/medicines/publications/PharmaNewsletter5-19/en/*

Glibenclamide: Risk of palpitations

Background: The NCC-PvPI, IPC has advised CDSCO to request the revision of the PIL for glibenclamide to include palpitations as an adverse drug reaction.

Issue: Glibenclamide is used for the treatment of diabetes mellitus. Between July 2011 and December 2018, NCC-PvPI received 12 ICSRs of glibenclamide associated palpitation. The NCC-PvPI also assessed 103 relevant reports from the WHO global database for reports of adverse events and the literature. A signal was published by the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC) which identified this reaction as a signal in the Asian population. The cases were reviewed by SRP at the NCC-PvPI, IPC, and a strong causal relationship between glibenclamide and palpitations was suggested.

Reference: *WHO Pharmaceuticals Newsletter. World Health Organization. 2019 [cited 4 December 2019]. Available from: https://www.who.int/medicines/publications/PharmaNewsletter5-19/en/*

MATCH THE FOLLOWING DRUG WITH ITS SPECIFIC ADR

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1	Dipyridamole	A	Acute psychosis
2	Irinotecan	B	Weight gain
3	Paclitaxel	C	Nasopharyngitis
4	Zoledronate	D	Pelvic cramps
5	Amiodarone	E	Skin rash
6	Olanzapine	F	Increased risk of Myocardial Infarction
7	Mefloquine	G	Severe diarrhea
8	Miconazole	H	Seizures with NSAIDs
9	Sitagliptin	I	Goiter
10	Loracarbef	J	Neutropenia
11	Flecainide	K	Shoulder Hand Syndrome
12	Etanercept	L	Blackouts in elderly
13	Ciprofloxacin	M	Coronary steal phenomenon in elderly
14	Isoniazid	N	Activation of latent tuberculosis
15	Midazolam	O	Osteonecrosis of jaw

Answers : 1-M; 2-G; 3-J; 4-O; 5-I; 6-B; 7-A; 8-D; 9-C; 10-E; 11-F; 12-N; 13-H, 14-K, 15-L

ALPHABET "W-X" PUZZLE

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1 W									
2	X								
3		X							
4			X						
5				X					
6					X				
7						X			
8							W		
9								W	
10									X

1. _____ ointment, a combination of Benzoic acid (6%) and Salicylic acid (3%), used for treatment of superficial fungal infections, is not systemically absorbed, so can be used safely during pregnancy.
2. Bisphosphonates are used to prevent loss of bone mineral density in postmenopausal women due to Aromatase Inhibitors like _____.
3. SLUDGE (Salivation, Lacrimation, Urination, Defecation, Gastric emptying, Emesis) is one of the _____ described in clinical toxicology in case of Organophosphate poisoning.
4. Antipyretics should be prescribed and Penicillin should not be discontinued when a case of secondary syphilis develops Jarisch _____ reaction after the first dose of Penicillin.
5. An increase in gout flares was frequently observed after initiation of therapy of this Xanthine oxidase inhibitor, due to sudden reduction in serum uric acid resulting in mobilization of urate from tissue deposits.
6. Live vaccines should not be administered to patients receiving this IL-6 antagonist (FDA approved for treatment of Castleman disease) because IL-6 inhibition may interfere with normal immune response.
7. There is a possibility of worsening of depression or suicidal ideation by this orexin receptor antagonist used for treatment of insomnia.
8. The appearance of a _____syndrome when administration of a drug is terminated, is the only actual evidence of physical dependence.
9. Acetylcholine was the "vagusstoff" discovered by the pharmacologist _____ who received Nobel Prize in 1936 for demonstrating chemical neurotransmission.
10. The most common adverse drug reactions (20%) when this BCL2 inhibitor is given in patients of CLL with Rituximab are neutropenia, diarrhea, fatigue and respiratory tract infection.

ALPHABET 'W-X' PUZZLE: ANSWERS :

1. WHITFIELD'S
2. EXEMESTANE
3. TOXIDROMES
4. HERXHEIMER
5. FEBUXOSTAT
6. SILTUXIMAB
7. SUVOREXANT
8. WITHDRAWAL
9. OTTO J LOEWI
10. VENETOCLAX

We would like to request all the clinical departments to contribute in ADR reporting.

Please feel free to contact us for the same.

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